Clinical trial roadmap

For sponsor (verrichter) of an Investigator Initiated Study (IIS)

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De volgende partijen hebben bijgedragen aan dit document:
Erasmus MC, IKNL, LUMC, NKI-AvL, RadboudUMC, MUMC

Proclaimer

De informatie in dit document is met de grootst mogelijke zorg en aandacht samengesteld door experts uit verschillende disciplines en samengebracht en ter beschikking gesteld vanuit DORP. Bij het samenstellen van de informatie is gebruik gemaakt van verschillende bronnen. Er is rekening gehouden met de op het moment van plaatsen geldende wet- en regelgeving en ethische kaders, en de interpretatie daarvan door de personen en/of organisaties die bijdragen aan DORP. We doen ons uiterste best om alle informatie juist en volledig weer te geven. Komt u desondanks toch iets tegen dat niet correct is of verouderd, dan stellen wij uw reactie bijzonder op prijs.

Inhoud

Introduction

The Clinical trial roadmap is developed by DORP to optimally support investigator initiated clinical oncological research. It is not unique as most trial and science offices have their own guidelines. This roadmap is however the result of exchanging and combining experience and knowledge of experts from Erasmus MC, IKNL, LUMC, NKI-AvL, RadboudUMC, MUMC. It brings together useful tips, references and links to templates.

The roadmap guides investigators through 6 phases of a clinical trial. It gives an overview of responsibilities and what needs to be organized. Importantly, at all times it should be used in conjunction with the investigator's local trial/science office.

The to do's differ for the initiating investigator (sponsor) and for participating local investigators. Therefore 2 versions of the roadmap are developed: one with to do's for the sponsor and one with to do's for participating centers. Every clinical trial phase is summarized by an infographic to illustrate the most important actions.

Before you start

This Roadmap is intended as a tool for starting up a clinical trial. To be able to set up a trial of high quality, it is of great importance for a Principal Investigator (PI) to have a valid BROK (preferably) or GCP certificate. The BROK training course focuses on methodology, project coordination and drafting of a protocol, in addition to knowledge about GCP. For collaborating and executing investigators in participating centers a valid GCP certificate is sufficient.

Contact the local trial/science office for information about local practice and available services within your institute, including datacenter, monitoring and statistics.

1 Phase 1: Preparation

1.1 Research proposal

- The PI has a valid BROK certificate or has registered for a BROK training. Re-register if necessary.
- Involve patients in both study design and conduct. Patients can improve the quality and relevance of research. In addition, it has a positive effect on the empowerment of patients, which increases the willingness to participate in clinical studies. Contact a patient organization for assistance with receiving input from patients, for example through a brainstorm session. More information about patient participation in clinical trials can be found on the DORP website.
- Write a research proposal/protocol synopsis with an inventory of:
    - proposed patient population
    - number of patients
    - in- and exclusion criteria
    - objectives
    - study design (phase, randomization)
    - treatment schedule

    - table with (extra) procedures – assessment schedule
    - side studies: which contracts are needed with central lab, couriers, etc. (=vendor management)
    - biobank
    - QoL: which specific questionnaires are applicable
    - Risk inventory: monitoring, blood samples that are not measurable, the number of suitable patients appears not to be sufficient or patients are not willing to participate.
- Determine if the study proposal meets the research focus of your department and institute and if the study will be supported.
- Contact the local science office and inquire about the local "research code":
    - The level of support provided by the local science office.
    - Make arrangements about internal logistics: who signs contracts, how are monitoring and statistics arranged, is the clinical trial database/eCRF built and maintained in- or externally, who submits the research file to MEC/Institutional Board/CTIS-portal, is the institute registered for CTIS in case of drug research, etc.
- Contact a datacenter for support for datamanagement, statistics, monitoring. Inform at the local science office which datacenter to contact.
- Contact the statistician about the study design and to calculate the number of patients needed. Consider timing of analyses, populations and subgroups to be analyzed, missing data, protocol deviations. Discuss costs and request a quote for the SAP (Statistical Analysis Plan) and analyses.
- Contact the monitor to discuss the study and to make arrangements about setting up the monitor plan. The NFU risk classification provides guidance. For studies that are according to NFU definitions classified as high risk by the sponsor or METC, the installation of a DSMB (Data Safety Monitor Board) is mandatory. Discuss costs and request a quote.
- Inform the tumor-specific research group (or relevant science committee) about the research proposal. Determine if there are comparable or competitive trials. Agree on whether or not the research group supports the study proposal. Discuss and agree on the role of the research group (sponsor yes/no).
- Install a writing committee to develop the protocol: appoint the PI and co-investigators in consultation with the research group. Please note: the sponsor PI cannot act as a local PI because of the assessment of SUSARs.
- Prepare a draft budget in consultation with the local science office. In addition to (extra) procedures, also take into account trial coordination, monitoring, statistics, trial database, datamanagement, Clinical trial Insurance (depending on the sponsor: UMC, general hospital, research group, etc), costs for patient participation and publication in a scientific journal.
- Include budget for planning, development, translation and dissemination of the layman's summary. For drug research it is required to upload the layman's summary in the CTIS-portal no later than 12 months from the end of the clinical trial,

1.2 Funding

- Determine if the start of the study depends on external financing.
- Determine which funding stream is used to fund the study: 1st/2nd/3rd/4th
  1st: Government grant; make agreements within department/ institute
  2nd: Independent public organizations, such as NWO and KNAW; apply for subsidy
  3rd: Collection box fund, such as KWF; apply for subsidy
  4th: Industry: have the contract looked at (content, finances, legal) by the legal department
- Make an inventory of which subsidy providers are available and determine at which one(s) to apply.
- Contact a relevant patient organization to give advice on the research proposal from a patient perspective. Most subsidy providers require a letter of support to be uploaded along with the research proposal.
- Collect what is needed to apply: protocol, PIF, (justification of) budget, quotes.
- Inform about grant conditions of the subsidy provider (pay attention to: in- or excl. VAT, is it allowed to spend it externally on services such as datamanagement or may it only be spent internally).
- Be aware of the conditions of the grant provider regarding the start date of the study. By exceeding this you risk to have to return the grant.
- In case of financing by a pharmaceutical company, discuss with them the protocol and budget, in collaboration with the local science office. It is often necessary for pharmaceutical companies to review the protocol, otherwise funding may be withdrawn.

1.3 Feasibility

- Check feasibility with regard to the number of available patients by a NKR data request based on in- and exclusion criteria. This manual contains guidelines how to request NKR data. The number of patients that actually want to participate in a study is always smaller than the number available. This depends on the (additional) study load and it is therefore important to have a good estimate of the feasibility. In general, divide the number of available patients by half to get a good estimate of the number of participants.
- Select sites in consultation with the research group. Site feasibility involves the number of available patients, the presence of a PhD student/study coordinator, local facilities and expertise. Collect commitment statements from institutes willing to participate. Be aware that potential local investigators must have a valid BROK/GCP certificate or are willing to attain this in short term (before the institute opens for the study).

1.4 Study design

- Write a study protocol using the CCMO template. Include items defined in the SAP, such as timing of analyses, populations and subgroups to be analyzed, missing data, protocol deviations. Consider how (S)AE's should be collected (for example by line listings).
- In parallel, write the PIF/IC using the CCMO template (protocol and PIF must be consistent, make changes simultaneously). This manual contains guidelines to make the PIF easier to understand.
- Contact the relevant patient association. Inform them about the study plan and ask who can review the PIF/IC. Also hand over questionnaires to be used in the study.
- Have the PIF/IC, questionnaires and eventual diaries reviewed by the patient association. Discuss and process suggested adjustments (readability, reduction of physical and mental burden).
- If applicable: write a nursing protocol.
- If applicable: write a lab manual.
- If applicable: compose a DSMB (Data Safety Monitor Board). Fill out a charter and have it signed. This is mandatory for research involving humans that is classified as high risk by the sponsor. The MEC often does not check this. Determine the risk level in consultation with the monitor.
- If applicable: prepare a plan including retention period of materials, requirements.
- Have the datamanagement, data validation and monitor plans made.
- In case of pharmacy involvement/distribution of medication, discuss costs and logistics.
- In case of storing samples in a biobank, determine where the biobank should be located and discuss costs and logistics with regard to transportation of samples.
- In case of central pathology: discuss costs and logistics with regard to the transportation of samples.
- In case of imaging reviews: discuss costs and logistics and record the procedure.
- Determine the submission date for CTIS (for review by the ethical committee).

1.5 Budget

- Identify the (extra) costs that will be made in the context of the study, based on the assessment schedule in the protocol and/or the table with (extra) clinical procedures in the VGO.
- If applicable: determine the start-up budget for the sites.
- Make an inventory if there will be costs for services such as trial coordination, monitoring, statistics, datamanagement (local and central), MEC, QoL.
- Request quotes for the required services (locally at the institute or at a service provider/ trial office when outsourced).
- Include costs for publication in a scientific journal in the budget.
- **Based on feasibility and budget, decide whether there is a "go or no-go".**

2 Phase 2: Start up and initiation

From February 2022 onwards, the procedures for local and central approval of *drug research* has changed and differs from the procedures for *other research subject to WMO* (overig WMO-plichtig onderzoek):

	Drug research	**Other research subject to WMO**
VGO	Mandatory from November 2021	Recommended from November 2021
OV	Not applicable from November 2021	Still accepted from November 2021
Registration	CTIS (Clinical Trial Information System)	Toetsingonline

Approval	Local (conditional!) followed by central MEC; central MEC approval & signed CTA turn conditional into full approval	OV: Central MEC followed by local VGO: Local (conditional!) followed by central MEC; central MEC approval & signed CTA turn conditional into full approval

The VGO (Verklaring Geschiktheid Onderzoeksinstelling) replaces the Research declaration (OV, Onderzoeksverklaring) and is used to record the outcome of the local feasibility meeting with involved departments about budget, logistics, etc., based on the overview of (extra) procedures provided by the sponsor. For details see the Local Feasibility procedure of the DCRF. For other research subject to WMO it is recommended to implement the VGO as soon as possible.

2.1 Research file & registration

- Check the CCMO website how to compose the standard research file. Preferably use the CCMO templates (protocol, PIF, cover letter, VGO, CTA) as these are generally accepted by ethical committees and science offices, etc.
- Follow the instructions for coding of documents as stated on the CCMO and MEC websites.
- An independent physician who can be contacted by patients with questions about the study is no longer required under the CTR. It is however still possible to make use of one. This has to be indicated in the cover letter and a CV has to be included in the application.
- In case of funding by a pharmaceutical company it is generally necessary for the company to review the protocol before submission, otherwise funding may be withdrawn. From February 2022 onwards clinical drug trial have to be registered in CTIS (Clinical Trial Information System). Training and support can be found at the EMA (European Medicines Agency) website.
- Self-register in CTIS to obtain access to secured workspaces within CTIS. Find more information about CTIS User Access Management in this Quick guide.
- Inform at your local science office if your organization (hospital) is or can be registered as sponsor organization in OMS/CTIS (so-called organization-centric approach). If so, you may request the clinical trial administrator within your organisation to assign roles to be able to perform actions within CTIS. In case your organization is not (willing to be) registered, you can apply the so-called trial-centric approach in which there is no sponsor administrator and management is done at trial level.
- Register the trial in the CTIS-portal, or discuss if this will be done by your local science office.
- Sign up the study at Onderzoekbijkanker.nl to have it published (for patients it will then automatically be published at kanker.nl). Text will be written in collaboration with the website editors and has to be approved by the MEC before publishing.

2.2 Contracts

- The CTA (Clinical Trial Agreement) is a contract between the sponsor and participating sites and should be provided by the sponsor. The current templates can be found on the CCMO website. Be aware to pick the right version applicable to your research. For drug research use:
  - Model research contract for use with VGO
- Use of this template is generally accepted and prevents delays. Pay attention to the maximum number of co-authors for future publications (first publication with all participating centers or as a group). The local science office can refer to the legal department to check the contract and negotiate if necessary. Leave this to the legal department.
- In case it is expected that patients will be referred to another institute for (part of) the treatment, for example for radiotherapy, the sponsor has to be informed and needs to make arrangements with that institute (because of GDPR (General Data Protection Regulation) or 'AVG' and insurance).
- In case of referring a patient to a non-participating center (for example for radiotherapy) the board of that institute needs to be informed that study patients are treated in their institute. The referring local PI is responsible that study procedures and data are recorded in the EPF of that institute and transferred to the local EPF.
- Contracts with other parties (pharmaceutical) should go through the legal department. In case of pharmaceutical involvement, have agreements included about publication of any data collected or generated, whether or not favorable for the medication under study.
- Contracts with internal/external service providers (monitoring, datamanagement, statistics) should go through te legal department. Pay attention to delegated tasks, including which party is responsible for archiving during the study, how and when to hand over the responsibility to the sponsor.
- If outsourced, inform how much time construction of the trial database will take. Construction can start as soon as the agreement with the constructor has been signed. Aim to have the trial database ready by the time the MEC gives approval so the study can start as soon as possible.
- Check with the local science office if processor agreements (verwerkersovereenkomsten) with parties that process data are signed. This only applies to external parties that process data and that are not covered by the standard CTA.
- In case of a biobank: confirm agreements about the retention period of materials, requirements.
- Start on time with the contracts.
- Clinical trial Insurance: the sponsor is responsible for the Clinical trial Insurance. Arrange this with the local science office. In the case of a multinational trial the sponsor has to ensure Clinical trial Insurances are arranged abroad.

2.3 Study team start-up

- Organize a study team start-up meeting to ensure the study team is and remains engaged and well-informed about expectations and responsibilities. The study team consists of PI, study coordinator, statistician, CDM, monitor).
  NB from end of March 2022 Toolkit Study preparation will be available from the DORP website.
- Define goals and end points of the study and determine what is needed to answer the research questions.
- Compose an item list for data collection in the eCRF, preferably in consultation with the central datamanager (if involved) constructing the trial database and eCRF and the statistician.
- The following items have to be connected and adjusted to one another, based on the protocol, to make sure the endpoints are collected and analyzed appropriately:
  - eCRF – electronic Case Report Form
  - SAP – Statistical Analysis Plan
  - DMP – Data Management Plan
  - DSMB – Data Safety Monitoring Board + Charter
- Identify potential risks and discuss how to handle those. Also identify potential risks that may need attention from the monitor.

2.4 Site suitability: VGO

- Make an inventory of centers to participate.
- Fill out the sponsor sections of the VGO, available from the CCMO.
- Inform the local PI's of participating centers about the trial and provide them with the protocol, global budget and partially filled-out VGO with overview of (extra) procedures, date of submission in the CTIS-portal.
- Emphasize the submission date in CTIS to the participating centers. In case sites do not respond in time they could be added later through an amendment but this will delay the start of those sites.
- Receive the signed VGO from participating centers before submission date or send reminders.
- ***Attention: a signed VGO means conditional Institutional Board approval from participating centers!***

In general for the sponsor's site as participating center

- In collaboration with the local science office, organize a local feasibility meeting to discuss the trial with involved departments in your institute. Provide sufficient detailed information. Think of the final protocol, list of (extra) procedures, budget, concept manuals.
- Make agreements with involved departments, document suitability of the institute in the VGO appendix and have it signed by involved departments.

- Have the VGO signed by the Institutional Board, thereby declaring the institutes' suitability based on the VGO appendix.
- ***Attention: a signed VGO means conditional Institutional Board approval!***

2.5 Approval

A. Central MEC approval

- Submit research file including VGO (from sponsor and participating centers) and template CTA in the CTIS-portal.
- Be available during the review period for RFI (Requests For Information) through the CTIS-portal or arrange back-up.
- Receive approval from the MEC through CTIS.
- Inform participating centers about study approval.
- Send the research file to the Competent Authority according to the CCMO instructions.

B. Local approval

- The Institutional Board has already given conditional approval by signing the VGO. This is converted into full approval once the CTA is signed and the MEC has approved the study.

During the MEC review procedure:

- Have the delegation logs signed by all participating centers. Send a copy to the trial office/central datamanagement to arrange accounts for registration/randomization of patients and access to the trial database. File the delegation logs in the TMF.
- Respond to MEC questions. At this time it should be clear when to expect approval.
- Plan the initiation visit locally and with the participating centers.
- Make the PIFs site-specific.
- Finalize logistics.
- Finalize budget.
- Sign contracts.
- Have the CTA finalized by the legal department and send them to participating centers.
- Check if signed CTA from participating centers are received.
- Finalize working documents (for example pharmacy manual) for and with the departments involved and share them with the participating centers.
- Compile the TMF: hard copy and/or according to local (digital) systems.
- Compile the ISF: hard copy and/or according to local (digital) systems and distribute to participating centers when the study documents are approved by the MEC.

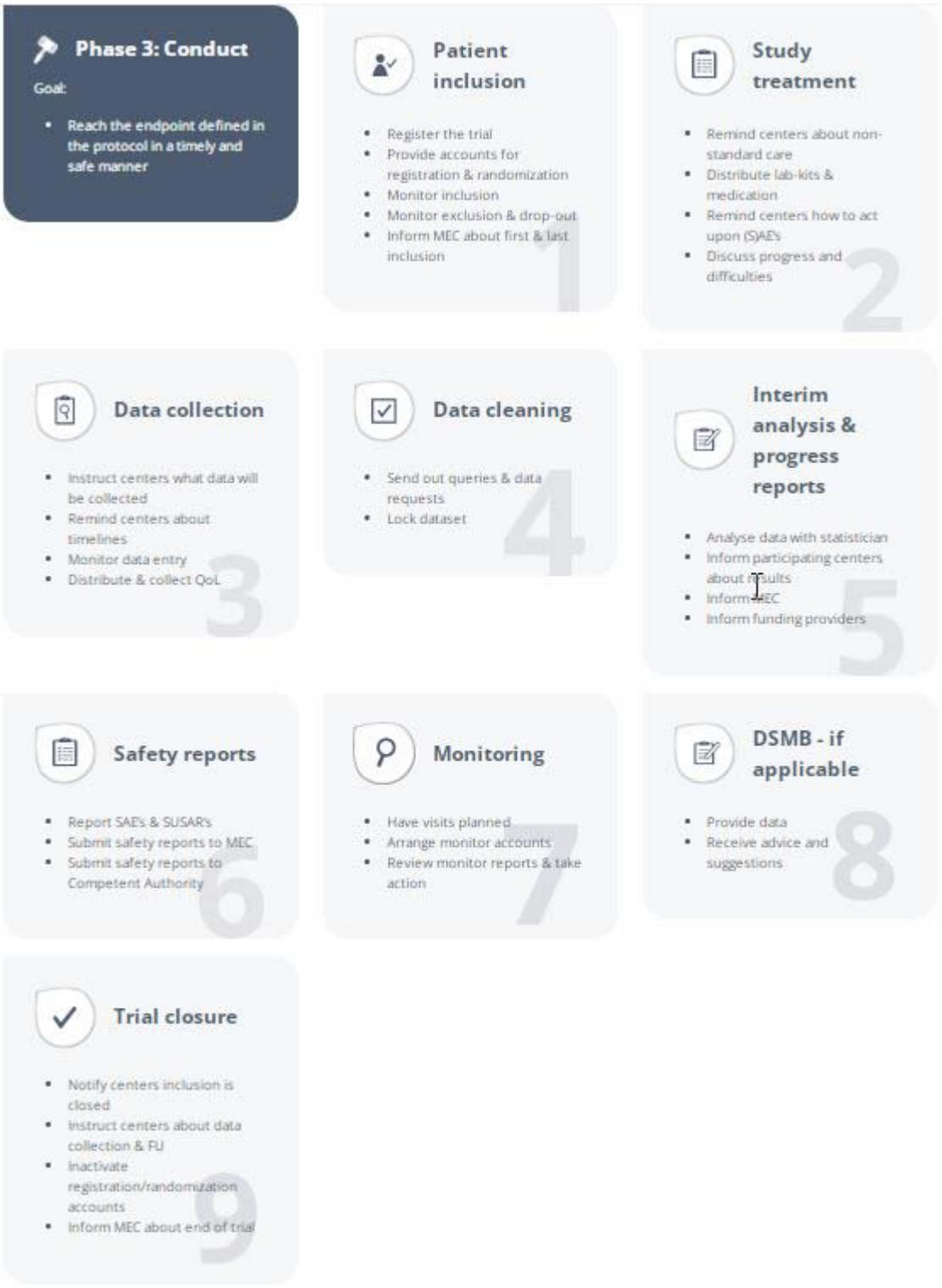
- In case of a multicenter study every site should receive an ISF. New essential documents (amendments, new versions of the protocol or PIF) should be sent when approved to archive in the ISF.
- Prepare 'zakkaartjes' if applicable.

2.6 Initiation

- After central MEC and local Institutional Board approval the initiation can take place: locally and in participating centers
- Invite participating centers. Request all involved departments to be represented.
- Have initiation log signed by all participants.
- Distribute 'zakkaartjes' if available.
- Inform participating centers that patients can only be informed after the site is initiated and received a start e-mail.
- Provide sites with instructions how to inform patients. Providing information via different channels (spoken, written, online) and at different moments can increase willingness of patients to participate.
- Instruct participating centers about patient inclusion. Before registering and/ or randomizing a patient, confirm the patient is eligible and fulfills the in- and exclusion criteria as patients cannot be withdrawn once randomized. Avoid erroneous inclusion as this effects the trial analysis. Provide instructions what to do in case of mistakes (for example contact study coordinator or CDM if involved).
- Instruct sites to register all eligible patients on the trial screening log to be able to monitor how many patients are eligible and informed about the trial and how many finally participate.
- Instruct sites about non-standard or extra care (extra blood or tissue samples, special tubes, scans, extra information to note in the EPF). Protocol deviations will make the data unevaluable. Instruct sites when in doubt to consult the PI or study coordinator.
- Distribute lab-kits, medication, etc. in time to participating centers. Make sure the local stock is replenished in time.
- Distribute instructions for taking, processing, sending or storing of (tumor) material.
- Distribute working documents to participating centers to instruct involved departments (pharmacy, radiotherapy).
- Provide instructions on how to handle baseline QoL.
- Inform what data will be collected in the eCRF to make sure all data is available in the EPF for source verification.
- Inform participating centers about the timelines for data entry. Timelines are maintained by CDM if involved, otherwise by a dedicated person from the coordinating center.

- Instruct participating centers how to handle (S)AEs. Because of timely SAE reporting it should be clear from the EPF if a patient takes part in a clinical trial (see also Phase 3: Safety reports, AEs, SAEs, SUSARs, SADEs).
- Check if the following has been arranged before a site can receive the start e-mail:
  -Local board and central MEC approval
  -CTA is signed
  -Delegation log is signed
  -Accounts (registration/randomization/eCRF) are arranged
  -Protocol signature page is signed
  -PIF is site-specific
  -Initiation visit has taken place and initiation log is signed
- Start e-mail can be sent (agree in advance on who sends this e-mail: trial database administrator, trial office, study coordinator). Once the start e-mail is received, the site is allowed to inform and include patients.

3 Phase 3: Conduct



3.1 Patient inclusion

- Register the trial in a trial registry: NTR or Clinicaltrials.gov, before inclusion of the first patient. Registration is made mandatory by several scientific journals to be able to publish.
- Have the study published on Onderzoekbijkanker.nl (for patients it will be published on www.kanker.nl) before start.
- Provide accounts for the registration and/or randomization program, or contact info (phone, e-mail) of the trial office appointed to register and/or randomize.
- Monitor inclusion by monthly accrual updates prepared by CDM (if involved) or study coordinator: which hospitals and local PI's include patients and which don't?
- Monitor exclusion: why are patients being excluded? If needed and possible, revise the protocol to be able to include a broader patient group. Protocol revisions should be approved by the MEC (substantial amendment) before implementation.
- Monitor drop-out. If needed and possible, revise the protocol to reduce drop-out. Protocol revisions should be approved by the MEC before implementation.
- Instruct sites to send appointment reminders to patients to prevent drop-out.
- Distribute newsletters (every 2-3 months) to all participating centers to inform them about accrual, points of attention and to create awareness about the trial.
- Follow up inclusion with participating centers by contacting them periodically to discuss progress.
- Contact PI's (preferably by phone) from participating centers that show insufficient inclusion to discuss why inclusion stays behind and to provide help.
- Inform the MEC when the first patient is included in the trial
- Inform the MEC when the last patient is included and inclusion is closed (the study and FU will continue).

3.2 Study treatment

- Remind participating centers about non-standard or extra care (extra blood or tissue samples, special tubes, scans, extra information to note in the EPF). Protocol deviations will make the data unevaluable. Instruct participating centers when in doubt to consult the PI or study coordinator.
- Distribute lab-kits, medication, etc. in time to participating centers. Make sure the local stock is replenished in time.
- Remind participating centers on how to act upon (S)AEs. Because of timely SAE reporting it should be clear from the EPF if a patient takes part in a clinical trial (see also Safety reports, AEs, SAEs, SUSARs, SADEs).
- Discuss progress and difficulties with study team and participating centers.
- Try to involve patients in the execution of the study (via a patient organization). This may be helpful when for example inclusion problems arise.
- Prepare amendments of protocol and PIF for MEC approval if needed

- Distribute (MEC approved) amended protocol and PIF versions as soon as possible to participating centers with instructions for implementation and to archive them in the ISF.
- Archive (new) documents in the TMF.
- Check if any amendment requires that patients should receive and sign a new version of the PIF/IC and instruct participating centers.
- Check if any amendment requires adjustment of instruction documents such as nursing/pharmacy protocols or manuals.
- Check if any amendment requires adjustment of the trial database and eCRF. In case this is outsourced to CDM, notify in advance and discuss costs.

3.3 Data collection

- Data will be collected in the eCRF. Depending on what is agreed this should be delegated to dedicated local datamanagers, the local PI or the local study team. If applicable, instruct participating centers to arrange that local datamanagers have a place to work, receive an institute account login and have permission to access the EPF of trial patients.
- Instruct participating centers what data to collect in the eCRF to make sure all data is available in the EPF for source verification.
- Remind participating centers about the timelines for data entry. Timelines are maintained by CDM if involved, otherwise by a dedicated person from the coordinating center.
- Monitor if data entry is correct and according to timelines and send out queries/data requests if needed by study coordinator or involved CDM.
- Distribute and collect QoL questionnaires on paper or electronically. Per patient these should be send out, returned and processed at fixed timepoints specified in the protocol. Agree with organization or person in charge on how to track this and when action is needed.
- Send out queries and data requests by study coordinator or involved CDM to keep data collection up to date.
- Remind participating centers for how long and at what frequency follow up and data collection continue after the trial is closed for inclusion.

3.4 Data cleaning

- eCRF database maintenance and data cleaning have to be done according to the data validation plan.
- Send out queries and data requests (by CDM if involved) for missing data or clarifications.
- Stay in contact with the monitor about the quality of data entry. Give (site specific) points of attention to the monitor to address during site visits.
- Inform participating centers when the trial database will be locked.

- Lock the dataset after confirmation that all missing data are explained and queries are resolved.
- Keep a secured file and open file to be able to go back to the original dataset.
- Before final trial closure, send out a final request to submit the latest data in the eCRF.

3.5 Interim analysis & progress reports

- It is defined in the protocol when an interim analysis should be scheduled. Send out a request on time (by CDM if involved) to participating centers to enter all required and available data into the eCRF database before a set deadline.
- Analyse data in close collaboration with the statistician.
- Keep an audit trail of the analysis to be able to trace the steps that have led to an outcome.
- If applicable, have the interim analysis reviewed by the DSMB (see 3.8).
- Decide if the trial continues or needs adjustment, based on the outcome of the interim analysis and DSMB advice.
- If required, modify SAP (statistical analysis plan) and the statistical section in the protocol in collaboration with the statistician.
- Inform participating centers about results (newsletter).
- Submit a progress report within 1 year after the analysis to the MEC through CTIS. If applicable, report the DSMB advice. If the sponsor decides not to follow the advice in full, the sponsor has to send the advice to the MEC. The reason for not following the advice should be explained in the cover letter.
- Inform funding providers by submitting a progress report.
- If required, amend the protocol and submit to the MEC for approval. Distribute (MEC approved) amended protocol and PIF versions as soon as possible to participating centers with instructions to implement and archive in the ISF.
- The sponsor is obliged to inform the review committee MEC at least once a year about the progress of the trial.
- In case of early termination of the trial, the review committee MEC needs to be informed.

3.6 Safety reports: AEs, SAEs, SUSARs,

- Provide instructions to participating centers how to register and report (S)AEs to the sponsor.
- AEs will be collected in the eCRF as defined in the trial protocol.
- SAEs should be reported to the sponsor within 24 hours after being discovered. In the trial protocol is defined what type of SAE does not require immediate notification.
- Include an aggregated table of SAEs in the Annual Safety Report (ASR) to be submitted to CTIS. Individual SAEs are not reported in CTIS.

- Submit SUSARs through Eudravigilance. If a SAE is suspected to be related to the IMP and is not described in the reference safety information, the SAE should be reported a SUSAR.
- Report serious breaches in CTIS within 7 days.
- Submit safety reports to the MEC about the research drug on a yearly basis, until the end of the study (usually the last visit of the last patient). The safety report can be combined with the annual progress report.
- If required, amend the protocol and submit to the MEC for approval. Distribute (MEC approved) amended protocol and PIF versions as soon as possible to participating centers with instructions to implement and archive them in the ISF.
- Report temporary halt or early termination of the study, for whatever reason, through CTIS.

3.7 Monitoring

- This Toolkit Monitoring contains useful templates and manuals.
- Have visits planned by the monitor according to the monitor plan, depending on onsite and centralized/remote monitoring.
- Arrange monitor accounts, also in participating centers. Permission for monitors to access the EPF is agreed upon in the CTA.
- The monitor checks if TMF and ISF are up to date (presence of all versions of protocol and PIF, delegation log, signed ICF for all patients, etc.).
- The trial is monitored depending on what is described in the monitor plan. In general the monitor checks:
    - for patients' rights, wellbeing and safety.
    - whether data is correct, complete and verifiable to source documents.
    - whether the conduct of the trial is in accordance with the current version of the protocol.
- Have monitor visit reports written by the monitor. The monitor communicates these to the involved site and the sponsor.
- Review monitor visit reports and take action if required.
- The monitor follows up findings described in the monitor visit reports and communicates to the sponsor.
- If applicable, the monitor prepares a report with specific points of attention for the DSMB.
- The monitor may comment on the risk assessment. This is not only about the risk for patients, but also about the chance of success of the trial, risk of protocol deviations due to complicated logistics, etc. Ultimately the sponsor is responsible for the risk assessment.
- Have DSUR available in case of drug research. The monitor checks for correct and timely DSUR.
- The monitor plans close out visits after LPLV for each site.

3.8 DSMB – if applicable

- The trial-specific DSMB charter, approved by the MEC before the start of the trial, describes the role and actions of the DSMB.
- The frequency of meetings depends on statistical analysis plans specified in the protocol, and otherwise on trial events. It is recommended that the DSMB meets at least yearly.
- Provide data to the DSMB according to the charter.
- The DSMB performs an interim review of the trial's progress including recruitment, data quality, and main outcomes and safety data.
- Receive advise on protocol modifications, such as inclusion criteria, sample size, endpoints.
- Receive suggestions for additional data analyses.
- The DSMB needs to report their recommendations and decisions to the Trial Steering Committee or sponsor's representative.
- Meet at the end of the trial to discuss the final data and advice given on data interpretation.
- Decide on following up on advice. In general, the advice of a DSMB is only sent to the sponsor. If the sponsor decides not to follow the advice in full, the sponsor has to send the advice to the MEC. The reason for not following the advice should be explained in the cover letter.

3.9 Trial closure

- Notify participating centers inclusion is closed.
- Instruct participating centers about follow up: for how long and at what frequency should data collection be continued.
- Instruct participating centers they have to inform their Institutional Board that the trial is closed for inclusion.
- Inactivate registration/randomization accounts.
- Notify participating centers when data collection and the follow up period are closed.
- Instruct participating centers they have to inform their Institutional Board the trial is closed for follow up.
- Inform the MEC about end of trial after completion of follow up. For drug research the MEC should be notified within 15 days after the trial has ended through CTIS.
- Send out queries and data requests for missing data or clarifications.
- Lock the dataset after confirmation that all missing data are explained and queries are resolved.
- Keep a secured file and open file to be able to go back to the original dataset.
- Register trial closure in the trial registry, NTR or Clinicaltrials.gov.
- Inform the editors from Onderzoekbijkanker.nl the trial is closed.

- Inform the Clinical trial Insurance company about LPLV and final number of included patients.

4 Phase 4: Analysis & publication

4.1 Statistical analysis

- Obtain all (cleaned) data collected as part of the clinical trial , and hand over to the trial statistician according to format and listings predefined in the SAP.
- Have the data analyzed by the trial statistician according to the SAP and the data analysis plan where the primary and secondary endpoints are defined. In the SAP is described what to do with data from ineligible patients/ screen failures. Attention should be paid to interpretation of intent to treat and consequences for analysis. An audit trail of the analysis should be kept to be able to trace the steps that have led to an outcome. The trial statistician provides a statistical report.

- Interpret and discuss the outcomes in the statistical report with the statistician and decide if additional analyses are needed.
- If applicable, organize a meeting with the DSMB at the end of the trial to allow the DSMB members to discuss the final data with the PI/sponsor and give advice about data interpretation.
- Define the answers to the primary and secondary endpoints.
- Determine the message/conclusion of the results.
- When applicable: define follow-up research questions and start a new trial with Phase 1.

4.2 Reports

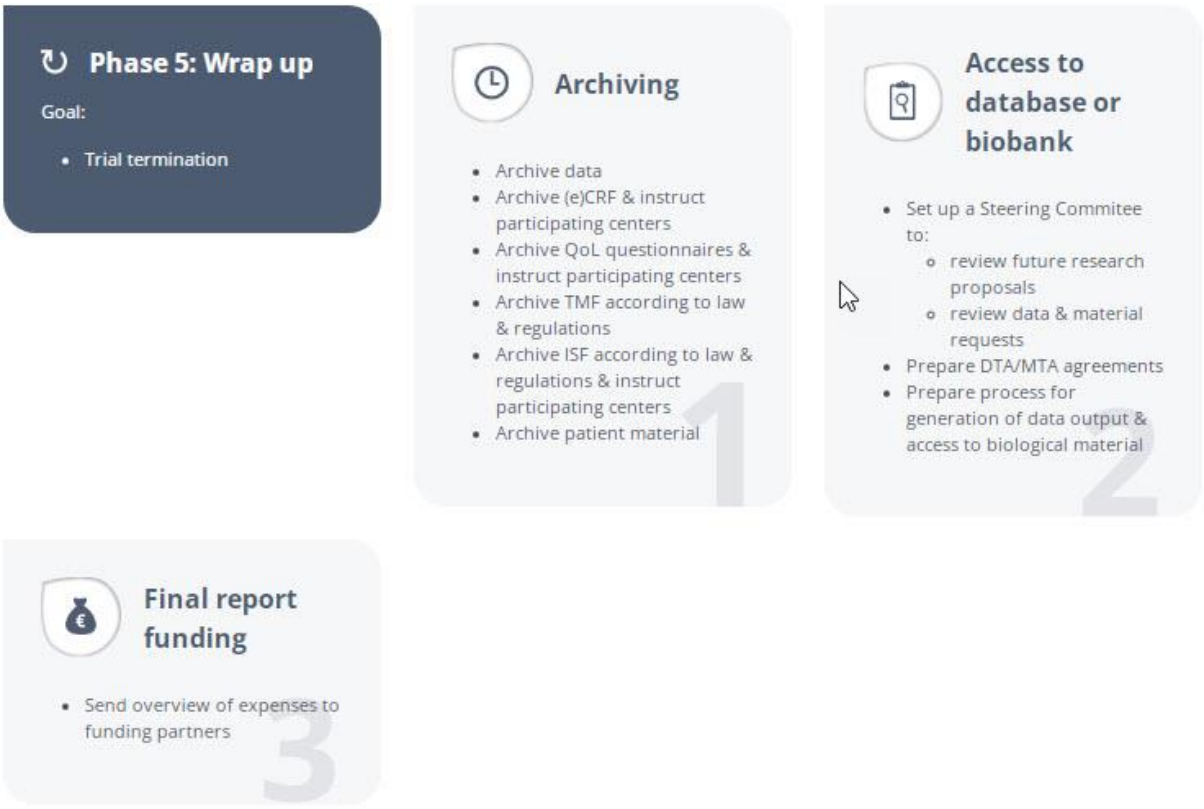
- Prepare a final report: a summary of the trial results has to be submitted to CTIS within 12 months after the trial is closed (worldwide).
- Prepare a layman's summary of the trial results and submit to CTIS within 12 months after the trial has closed (worldwide). Patient advocates who are involved during the study can provide help and advice. Check practical guidelines on the DORP website or the extensive guidelines from the Roadmap Initiative to Good Lay Summary Practice Group.
- Have the layman's summary published at Onderzoekbijkanker.nl (for patients it will then be published at kanker.nl).
- Sponsors are obliged to post results in the European Clinical Trials Register for any interventional trial registered in the EudraCT database.
- Report to funding partners according to agreements.

4.3 Manuscript preparation & publication

- Decide how and where to publish the results (what medium: conference abstract, peer reviewed journal, open source platform, national professional magazine). Be aware about the criteria for publication and publication costs.
- Interpret and discuss results with project team/ protocol writing committee/co-authors.
- Check agreements/contracts with funding partners prior to publication of results and discuss publication in a timely manner with involved parties. Check in agreements/contracts if there are no objections to publish any info collected or generated by the investigators, whether or not the results are favorable to the medication under study.
- Publications will be joint publications with the participating centers. Since the number of co-authors may be restricted by the journal, publication as a group has to be considered. Check what is agreed on in the CTA.
- Preferably, involve patient advocates engaged to the study to help with the interpretation and formulation of research results (from a patient perspective).
- Prepare manuscript according to instructions provided by the publisher.
- Have the manuscript reviewed by co-authors and collect non-disclosure forms when applicable.

- Have the manuscript reviewed by funding partners if applicable/obliged.
- Give the sponsor the opportunity to review any proposed publication or any type of disclosure before it is submitted or otherwise disclosed.
- Submit the manuscript to the publisher.
- Respond to review comments if requested.
- When accepted for publication, inform co-authors and funding partners.
- Optional: Have a press release prepared by the local communication/PR department. Prior to publication, have the press release reviewed by the research group and patient association so they are informed and prepared and have the opportunity to make nuances to the message.
- Write a layman's summary and upload this in CTIS within one year after trial closure. This is obliged to comply with the CTR. Check practical guidelines on the DORP website or the extensive guidelines from the Roadmap Initiative to Good Lay Summary Practice Group.
- Publicly disclose the results in a clinical trial registry, such as www.trialregister.nl, www.clinicaltrials.gov or the CCMO registry.
- Update information on Onderzoekbijkanker.nl by providing trial results to the website editors: have the layman's summary published at Onderzoekbijkanker.nl (for patients it will then be published at kanker.nl).
- It is recommended to inform included patients about the results, by means of a patient letter in which the patient is thanked for participation, (provisional) results are given and information about where follow-up results can be found is provided.
- Inform patient organizations about the results. They can help with the distribution of the results (e.g. translating the results in understandable language and thinking about/helping with implementation of the results).

5 Wrap up



5.1 Archiving

- Archive data: dataset with audit trail used for analysis, as well as the original dataset. Be aware of and adjust how long data should remain available, for example when follow up period is expanded.
- Archive (e)CRF and instruct participating centers how to archive, if applicable.
- Archive QoL questionnaires and instruct participating centers how to archive.
- Archive TMF/research file for verification purposes (e.g. in the context of inspections), for the duration of the predetermined retention period, commencing after the last visit (or research related activity) from the last patient worldwide. Storage period depends on the type of trial (drugs, WMO-plichtig) and law and regulations. Directly traceable data must be stored separately from the encoded data. For drug research the TMF should be stored for 25 years.
- When the predetermined retention period has expired, the TMF/research file has to be destructed on the instructions of the sponsor. Traceable documents and research data have to be irretrievably deleted.
- Archive ISF and instruct participating centers to archive their ISF after the study is closed, commencing after the last visit (or research related activity) from the last patient worldwide. Storage period depends on the type of trial and law and regulations. Directly traceable data must be stored separately from the encoded data.

- Archive patient material (locally or in biobank) according to predetermined retention period and requirements and instruct participating centers. Storage period depends on law and regulations.

5.2 Access to database or biobank (when applicable)

- Maintain or set up a Steering Committee (SC) for the purpose of:
  - Review new proposals of correlative research or additional analysis not planned in the protocol ("future research") and decide on the appropriateness to pursuit them.
  - Review requests for access to trial data and material (provided that the informed consent allows such).
  - Review proposals to exchange data for meta-analyses.
- Prepare DTA/MTA between sponsor and requester.
- Prepare a process for generation of data output and/or access to provide biological material.

5.3 Final report funding

- Send overview of expenses to funding partners (final report).

6 Implementation or follow up research

Investigator initiated phase II/III trials do not always provide the level of evidence needed to adjust guidelines, but can give indications for further research. The following steps are optional and depend on the trial results.

6.1 Implementation

- Contact representatives of the (multidisciplinary) profession(s) to discuss implementation of the trial results.
- Provide representatives of the (multidisciplinary) profession(s) with additional data when necessary for implementation of the results and /or discussions with health insurance by the representatives.
- Contact health insurances via representatives of the (multidisciplinary) profession(s).
- Bring the results to the attention of colleagues/profession group by publications in medical/scientific journals, presentations at meetings, mailings, questionnaires.
- Inform representatives of patient organizations to bring the results to the attention of patients.
- Evaluate implementation.

6.2 Follow up research

- Develop follow up research plan, see Phase 1.

7 List of abbreviations

BROK	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers
CCMO	Competent Authority (Centrale Commissie Mensgebonden Onderzoek)
CDM	Central Datamanagement
CRO	Clinical Research Organisation
CTA	Clinical Trial Agreement
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
DTA	Data Transfer Agreement
(e)CRF	electronic Case Report Form
EMA	European Medicines Agency
EPF	Electronic Patient File (=EPD)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IC	Informed Consent
ISF	Investigator Site File
LDM	Local Datamanagement
LPLV	Last Patient Last Visit
MDO	Multidisciplinairy consultation (Multidisciplinair overleg)
MEC	Medical Ethics Committee
MTA	Material Transfer Agreement
NKR	Nederlandse Kanker Registratie
NTR	Netherlands Trial Register
OMS	Organization Management System
OV	Onderzoeksverklaring
PI	Principal Investigator
PIF	Patient Information Folder
QoL	Quality of Life
RFI	Request For Information
SAP	Statistical Analysis Plan
TMF	Trial Master File
WMO	Wet Medisch-wetenschappelijk Onderzoek met mensen